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Early Onset Cannabis Use and Progression to other Drug Use in a Sample of Dutch Twins

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One possible explanation of the commonly reported associations between early onset cannabis use and elevated risks of other illicit drug use is that early onset cannabis use increases access and availability to other drugs. It was this argument that in part motivated policy changes in the Netherlands that led to the de facto legalization of cannabis there. This study examines, using a co-twin control design, whether previously observed associations between early onset cannabis use and elevated lifetime rates of other illicit drug use would also be observed in a sample of 219 same sex Dutch twin pairs discordant for cannabis use before age 18. After adjustment for covariates, rates of lifetime party drug use (OR = 7.4, 95% CI = 2.3–23.4), hard drug use (OR = 16.5, 95% CI = 2.4–111.3), but *not* regular cannabis use (OR = 1.3, 95% CI = 0.3–5.1) were significantly elevated in individuals who reported early onset cannabis use, relative to their co-twin who had not used cannabis by age 18. The elevated odds of subsequent illicit drug use in early cannabis users relative to their non early using cotwins suggests that this association could not be explained by common familial risk factors, either genetic or environmental, for which our co-twin methodology provided rigorous control.

KEY WORDS: Cannabis; other illicit drug use; twins, gateway theory; The Netherlands.

One of the most enduring controversies in drug research and policy concerns the extent to which early cannabis use may predispose to the use of other “hard” drugs such as cocaine and heroin (Kleiman, 1992; MacCoun, 1998). Stage theory posits that there is an invariant sequence in drug use with onset of use falling along a continuum with the licit drugs (tobacco, alcohol) being used before cannabis, which in turn precedes the use of other drugs such as cocaine and heroin (Kandel, 1975; Kandel and Faust, 1975). While such a sequence has been observed in numerous studies

(Collins, 2002; Ellickson *et al.*, 1992; Graham *et al.*, 1991; Kandel *et al.*, 1992; Kandel and Yamaguchi, 2002), the interpretation of such findings remains controversial. Specifically, some researchers have argued that cannabis plays a causal role in the escalation to other drug use and that therefore delay or avoidance of cannabis use would reduce – or even eliminate – risks of the subsequent use of other drugs (DeWit *et al.*, 2000; Kosterman *et al.*, 2000). Conversely, it has been argued that the observed associations may simply reflect a combination of common underlying vulnerabilities to substance use in general (Baumrind, 1983; Morral *et al.*, 2002) and levels of availability and access to different drug classes (Wagner and Anthony, 2002; Wilcox *et al.*, 2002). Controversy surrounding this issue is not solely of academic interest: the alleged gateway effects of cannabis have been used as a major rationale for the continued legal prohibition of that drug in the US and many other countries.

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Tests of this hypothesis require that patterns of other drug use be compared in people who differ in no respects other than their use of cannabis. Several studies have attempted to achieve such control using statistical adjustments and have reported that early cannabis use remains a risk factor for the subsequent use of other drugs (Fergusson and Horwood, 1997, 2000; Yamaguchi and Kandel, 1984). Similarly, we recently reported analyses using a genetically informative design comparing rates of other drug use and drug abuse/dependence in Australian twin pairs discordant for early cannabis use (before the age of 17 years; Lynskey *et al.*, 2003). Such a design provides a rigorous test of the hypothesis that early cannabis use influences risks of later drug use and drug/abuse dependence as, for twin pairs raised together, as was our Australian sample, aspects of the home and family environment do not differ and, in the case of monozygotic twins, members of each pair are genetically identical. Thus comparisons within twin pairs are likely to achieve a more rigorous control of potentially confounding covariates than reliance on statistical control of observed covariates assessed in non-related individuals. Our results indicated that individuals who used cannabis by age 17 had odds of other drug use and drug abuse/dependence that were 2.1–5.2 times higher than those of their co-twin who did not use cannabis before age 17.

There are a number of possible mechanisms that may underlie this observed association. Firstly, research indicates that Δ^9 – tetrahydrocannabinol and heroin have similar effects on dopamine transmission through a common μ_1 opioid receptor mechanism (Tanda *et al.*, 1997) and that chronic treatment with Δ^9 – tetrahydrocannabinol induces cross-tolerance to amphetamine (Lamarque *et al.*, 2001) and opioids (Cadoni *et al.*, 2001; Lamarque *et al.*, 2001) in rats. However, it is unlikely that biological mechanisms could plausibly explain the observed associations as the extent of cannabis use among young people is typically quite low and infrequent, and is certainly substantially lower than the equivalent doses used in animal research. Alternatively, it is possible that the mechanisms underlying the observed association are largely social in nature. In particular, it has been argued that early access to cannabis may provide heightened access to and exposure to other illicit drugs. Indeed, it was this argument that provided the impetus for the Netherlands to effectively decriminalize cannabis use in the 1970s in an attempt to separate the cannabis and “hard” drug markets. Thus, if the factors underlying the observed

associations between early onset cannabis use and subsequent use of other illicit drugs arise principally from the legal status of cannabis, with early access to cannabis being associated with increased access to other illicit drugs, it would be hypothesized that the association between early onset cannabis use and the use of other illicit drugs would reduce or disappear in societies such as the Netherlands where cannabis is readily available while other drugs remain illegal.

As a test of this hypothesis, therefore, it is of interest to explore whether the effects observed in our Australian sample of twins would also be observed in a sample from the Netherlands. Accordingly, the aims of this paper are to use a discordant twin design to compare rates of other illicit drug use in individuals reporting early onset cannabis use and their co-twins who did not use cannabis at an early age.

METHOD

Sample

The data presented in this paper are part of an ongoing twin family study on health-related behavior of the Netherlands Twin Register (NTR) that assesses families with adolescent and young adult twins every 2/3 years since 1991 (Boomsma *et al.*, 2002). For the present study, the data from the 1995 and the 2000 surveys were used. In 1995, 3415 twins participated in the study and 4610 twins completed the 2000 survey. The total sample contained 6228 twins and 1800 twins participated in both waves. Average age at most recent interview was 26.75 years (SD 11.8). While there was wide variation in the age range of the sample, almost 75% of the sample was born between 1965 and 1980.

Measures

Cannabis Use

Lifetime use of cannabis was reported by 21.6% of the sample. Self-report data on age of first cannabis use from waves 3 to 5 were combined so that an individual who reported early onset cannabis use (before age 18) at either wave 3 or wave 5 was classified as an early onset user: 12.5% (544) reported initiating cannabis use before the age of 18 years. Of these, 219 (40.3%) were from same-sex twin pairs in which their twin did not report having used cannabis by the age of 18 and it is this subsample of discordant twins that is included in the current analysis. Opposite sex twins discordant for early onset cannabis use

were excluded from the current analyses because documented sex differences in the prevalence of illicit drug use suggest that sex may be one important factor associated with both early onset cannabis use and subsequent illicit drug use: comparison of rates of illicit drug use in opposite sex twins would therefore not control for this potentially important source of confounding. The final sample comprised 45 MZ male twin pairs; 63 DZ male twin pairs; 65 MZ female twin pairs and 46 DZ female twin pairs.

Other Drug Use

Lifetime drug use was assessed for the following drug classes: party drugs (reported by 3.3% of the analysis sample) and hard drugs (reported by 2.3% of the analysis sample). As for the assessment of early onset cannabis use, an individual reporting any lifetime use of party or hard drugs at either waves 3 or 5 was classified as having used these drugs.

Regular Cannabis and Other Illicit Drug Use

In addition to reports of any lifetime use, 3.6% of the analyzed sample reported *regular use* of cannabis and this measure was included as an outcome in the current analyses. Regular use of both party drugs and hard drugs was also assessed. However, such use was reported *only* by those who had used cannabis by age 18 years. Given this, these outcomes were excluded from the current analyses. Of course, it could be argued that the fact that only those who had used cannabis before age 18 reported regular use of both types of drugs provides compelling support for the hypothesis that early cannabis use influences risks of subsequent regular drug use.

Observed Covariates

To further control the associations between early cannabis use and subsequent illicit drug use a range of measures of early substance use and rule breaking behavior were included in the analyses. These measures were:

1. Regular tobacco use before age 18.
2. Regular alcohol use before age 18.
3. Aggressive behavior assessed in wave 5 using subscales of the Young Adult Self Report (YASR; Achenbach, 1997), translated into Dutch and validated by Verhulst *et al.* (1997).

4. Rule breaking behavior, again assessed at wave 5 using subscales of the Young Adult Self Report (YASR; Achenbach, 1997), translated into Dutch and validated by Verhulst *et al.* (1997).

Statistical Analyses

All statistical analyses were conducted using SAS (SAS Institute, 1996) and Stata (StataCorp, 1999). Conditional logistic regression models were fitted to test for excess risk among early onset cannabis users from discordant pairs, compared to their co-twin controls. Data from unlike-sex pairs and singletons were excluded. The significance of the interactions between early cannabis use and both twin pair zygosity and gender were tested and, as these were non-significant, data were pooled across zygosity, and across gender. Analyses were repeated including the covariate factors described above (early tobacco and alcohol use, aggressive and rule breaking behavior). Stepwise regression with backward selection was conducted with the measure of early cannabis use forced into the model. These analyses were used to estimate conditional odds ratios for hard drug use, party drug use and regular cannabis use in twins discordant for early cannabis use after control for other significant predictors.

RESULTS

The first two columns of Table I show estimates of the lifetime prevalence (%) of party drug use, hard drug use and regular cannabis use for those initiating cannabis use before age 18 and for their co-twins (who either reported no lifetime cannabis use or who reported initiating cannabis use at age 18 or older). The table also shows that, before adjustment for covariates, odds of party drug use (OR = 6.8, 95% CI = 2.7–17.4) hard drug use (OR = 14.0, 95% CI = 3.3–58.8) party and/or hard drug use (OR = 6.3, 95% CI = 2.7–15.0) and regular cannabis use (OR = 4.7, 95% CI = 2.1–10.7) were significantly higher in those who used cannabis before age 18 than in their co-twins who did not report early cannabis use. However, after adjustment for covariates (principally other early onset substance use and rule breaking behavior) there was no significant association (OR = 1.3, 95% CI = 0.3–5.1) between early cannabis use and later risks of regular cannabis use, although significant associations remained between early onset cannabis use and the use of party and/or hard drugs.

Table 1. Drug Use Outcomes in Twin Pairs Discordant for Cannabis Use before Age 18 (234 pairs)

	Lifetime prevalence		Odds ratios (95% CI)		
	Early cannabis users (%)	Co-twins (%)	Unadjusted	Adjusted	Significant covariates ^a
Use					
Party drugs	16.2	3.8	6.8 (2.7–17.4)	7.4 (2.3–23.4)	1
Hard drugs	12.8	1.7	14.0 (3.3–58.8)	16.5 (2.4–111.3)	1
Any party/Hard drug use	17.9	4.3	6.3 (2.7–15.0)	6.5 (2.4–17.9)	1
Regular use					
Cannabis	16.2	5.1	4.7 (2.1–10.6)	1.3 (.3–5.1)	1,2

^aSignificant covariates: 1 = rule breaking behavior (wave 5); 2 = early regular tobacco use.

Although not shown in the table, early onset of cannabis use was also associated with elevated rates of regular party drug use and regular hard drug use: 6.4% of early cannabis users reported regular party drug use and 5.1% reported regular use of hard drugs while none of their co-twins reported such use.

DISCUSSION

The results of our study indicated that young people who initiated cannabis use before age 18 were at heightened risk for the subsequent use of other drugs, relative to their co-twin who did not initiate cannabis use before age 18. Notably, while 5.1–6.4% of early cannabis users reported regular use of party or hard drugs, none of their co-twins reported such use. Our use of the co-twin control methodology provides a powerful methodology for controlling for the effects of potentially confounding familial factors that may act to predispose young people both to early cannabis use and to the subsequent use of other illicit drugs. While traditional research designs typically attempt to control for such sources of confounding through statistical control of observed covariates, we believe that the co-twin control methodology provides more stringent control for familial sources of confounding. This is especially true among discordant MZ twin pairs, who comprised fully half of our sample.

There are several caveats that need to be considered when interpreting these results. Firstly, the observation that familial factors do not entirely explain the association between early cannabis use and subsequent cannabis use, while suggesting a potential causal role for cannabis use in the development of other illicit drug use, does not prove such as an association. Specifically, there may be other factors, especially aspects of the non shared environment (e.g., peer affiliations) preceding the onset of cannabis use that might account for the observed associations.

Secondly, it remains possible that early onset cannabis use may be associated not with an increased risk for lifetime illicit drug use but with an earlier onset of such use. While possible, we consider this unlikely as the average age of the sample exceeds the period of maximum risk for the initiation of drug use. Finally, our study results rely critically on self report data and it is possible that such reports may be biased in some way. Nonetheless, the available research evidence supports the use of self-reported age of onset of cannabis use as these reports have been shown to have acceptable reliability and validity (Cottler *et al.*, 1989; Grant *et al.*, 1995) and that age at which substance use was assessed did not moderate the associations between age-of-onset and substance use related outcomes (Parra *et al.*, 2003).

Our results parallel earlier findings from an Australian sample (Lynskey *et al.*, 2003) and suggest that observed associations between early cannabis use and later drug use are unlikely to be due to the effects of familial factors predisposing to both early cannabis use and to the use of other illicit drugs. Furthermore, our replication of the previous results in a society in which legal sanctions against the use of cannabis are not applied suggests that these associations are not solely due to legal factors surrounding the context in which cannabis is used and obtained. They do not, however, discount social mechanisms as the mechanisms underlying these associations. Specifically, despite the liberal approach to cannabis use in the Netherlands, rates of cannabis use are substantially lower in that country than in Australia, the US and many other countries. For example, a recent study comparing rates of drug use in seven countries (Vega *et al.*, 2002) noted that the lifetime rate of cannabis use in the Netherlands (12.3%) was less than half of that in the US (28.8%) while a comparable estimate for Australia is that 39.3% of the adult population have used cannabis (Australian Institute of Health and Welfare, 1999). Thus, cannabis use

may represent a norm-violating and unconventional behavior in the Netherlands in much the same way as it does in Australia and other countries that adopt more punitive legal approaches to cannabis.

The results of this study hopefully will reduce the controversy surrounding the influence of early cannabis use on the subsequent use of other drugs. Irrespective of the causal process assigned to the observed effects, it is apparent that young people who initiate cannabis use at an early age are at heightened risks for the use of other drugs and the development of drug abuse/dependence. Interventions could therefore be usefully targeted at such individuals in an attempt to decrease the risks that they will progress to the use of other drugs and/or drug abuse/dependence.

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